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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/660,607	09/12/2003	David H. Mack	003848.00131	7415

28315 7590 05/31/2006

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EXAMINER	
SCHLAPKOHL, WALTER	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 05/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/660,607	MACK, DAVID H.	
	Examiner	Art Unit	
	Walter Schlapkohl	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *46-94* is/are pending in the application.

4a) Of the above claim(s) *50-59,63,64,74-84,87 and 88* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46-49,60-62,65-73,85,86 and 89-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 September 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/12/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of the papers filed 3/7/2006 in which claims 18-28, 39-40, 44-45, 95-106 and 109-129 were canceled. Claims 46-94 are pending. Claims 46-49, 60-62, 65-73, 85-86 and 89-94 are under examination in the instant Office Action.

Election/Restrictions

Claims 50-59, 63-64, 74-84 and 87-88 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/7/2006.

The restriction is still deemed proper and is therefore made FINAL.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because sequences are set forth in the

drawings that lack sequence identifiers. Specifically, Figure 5 sets forth both nucleic acid and protein sequences that lack sequence identifiers. It is often convenient to identify sequences in figures by amending the Brief Description of the Drawings section (see MPEP 244.02). If the sequences are already present in the sequence listing, it would be remedial to amend the Brief Description of the Drawings to include the appropriate sequence identifiers. Applicants are required to comply with all of the requirements of 37 CFR 1.821 - 1.825. Any response to this office action that fails to meet all of these requirements will be considered non-responsive. The nature of the noncompliance with the requirements of 37 C.F. R. 1.821 through 1.825 did not preclude the examination of the application on the merits, the results of which are communicated below.

Specification

The disclosure is objected to because of the following informalities: The description of Figure 8 on page 7 in the "Brief Description of the Drawings" section does not make reference to Figures 8A and 8B separately.

Appropriate correction is required.

Claim Objections

Claims 49, 60, 65 and 73 are objected to because of the following informalities: claims 49, 60, 65 and 73 read on non-elected subject matter. Appropriate correction is required.

Claim 90 is objected to because it is identical to claim 89.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 46, 65-71 & 89-94, and therefore dependent claims 47-49, 60-62, 72-73 & 85-86, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 46 recites "[a] method for determining loss of function of a nucleic acid encoding a regulatory molecule in a test cell comprising" in lines 1-2 and "identifying a test cell as having lost function of the regulatory molecule" in line 12. Claim 46 is vague and indefinite in that it is unclear whether Applicant intends a method for determining loss of function of a nucleic acid encoding a regulatory molecule, loss of function of

the regulatory molecule itself, or both. It appears from the preamble, that Applicant intends a method of determining loss of function of a nucleic acid encoding a regulatory molecule; however, line 12 would seem to indicate that the method is for determining lost function of the regulatory molecule itself.

Claims 65-66 and 89-90 refer to sets of genes "as defined in Table 2." Claims 65-66 an 89-90 are vague and indefinite in that the metes and bounds of any gene "as defined in Table 2" is unclear. For example, Table 2 refers to Thrombospondin as "Inhibitor of angiogensis" [sic]. Does Applicant intend to limit the throbospondin gene to those variants that inhibit angiogenesis or does Applicant intend to encompass a thrombosponding gene in any sequence variation and with any thrombosponding function?

Claim 67 recites "[t]he method of claim 46 further comprising the step of: determining the sequence of p53 genes in the test cell to confirm the p53 status of the cell" in lines 1-2. Claim 67 is vague and indefinite in that the metes and bounds of the phrase "p53 status of the cell" are unclear. Does the p53 status of the cell encompass the identification of the full-length sequence of both copies of p53 in a wild type cell or does p53 status refer to a partial sequence determination of expressed p53?

Claim 68 recites the phrase "the method of claim 46 wherein a test cell is identified as p53-negative if hybridization is at least 3-fold different between compared samples" in lines 1-2. Claim 68 is vague and indefinite in that it is unclear which samples are being compared with regard to hybridization. Does Applicant intend such a method wherein a test cell is identified as p53 negative if each one of the set of nucleic acid probes is hybridized to a transcription indicator and wherein hybridization of all probes tested is at least 3-fold different between compared samples, or does Applicant intend such a method wherein hybridization to only one of the probes need be tested? Which probes and which test cells are included in the comparison? Would the test cell be identified as "p53-negative" if the amount of hybridization were 3-fold LOWER in a test sample as compared to a normal sample?

Similarly, claims 69-70 recite such a method wherein a test cells identified as p53-negative if hybridization is at least 5- or 10-fold different between compared samples. Claims 69-70 are vague and indefinite in that it is unclear which samples are being compared with regard to hybridization as explained above.

Claims 68-70 are also vague and indefinite in that the metes and bounds of "p53-negative" are unclear. Does Applicant intend to encompass cells which express non-functional or mutant

p53, cells wherein p53 has been deleted, or cells in which p53 is simply not expressed or expressed at extremely low levels?

Claim 71 recites "[a] method of diagnosing neoplasia of a test cell comprising...identifying a test cell as neoplastic if (1) hybridization of the transcription indicator of the test cell to a probe which is a p53-activated gene is lower than hybridization using a transcription indicator from a normal cell, or (2) hybridization of the transcription indicator of the test cell to a probe which is a p53-repressed gene is higher than hybridization using a transcription indicator from a normal cell. Claim 71 is vague and indefinite in that the metes and bounds of a neoplasia/neoplastic cell are unclear. Does Applicant intend any abnormal new growth of tissue or does Applicant intend to encompass only malignant cancerous tumors? Claim 71 is also vague and indefinite in that it is unclear which p53-activated genes would be used in a test of "lower" or "higher" hybridization if the results between two or more p53-activated or p53-repressed genes were conflicting. Would each p53-activated or p53-repressed gene present as a probe have to show the same compared ratio of hybridization or does Applicant intend to encompass only one p53-activated or p53-repressed probe in the claimed method?

Claim 91 recites "[t]he method of claim 71 further comprising the step of: determining the sequence of p53 genes in the test cell to determine the p53 genotypic status of the cell" in lines 1-3. Claim 91 is vague and indefinite in that the metes and bounds of the phrase p53 genotypic status" are unclear. Does Applicant intend a "p53 genotypic status" wherein the identification of the full-length sequence of both copies of p53 in a wild type cell is determined, or does "p53 genotypic status" refer, e.g., to a deletion of one or both copies of p53 or aneuploidy resulting in multiple copies of p53 within a cell?

Claim 92 recites "[t]he method of claim 71 wherein a test cell is identified as neoplastic if hybridization is at least 3-fold different between compared samples. Claim 92 is vague and indefinite in that in that it is unclear which samples are being compared with regard to hybridization. Does Applicant intend such a method wherein a test cell is identified as neoplastic if each one of the set of nucleic acid probes is hybridized to a transcription indicator and wherein hybridization of all probes tested is at least 3-fold different between compared samples, or does Applicant intend such a method wherein hybridization to only one of the probes need be tested? Which probes and which test cells are included in the comparison? Would the test cell be identified as "neoplastic"

if the amount of hybridization were 3-fold LOWER in a test sample as compared to a normal sample?

Similarly, claims 93-94 recite such a method wherein a test cells is identified as neoplastic if hybridization is at least 5- or 10-fold different between compared samples. Claims 93-94 are vague and indefinite in that it is unclear which samples are being compared with regard to hybridization as explained above.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 46-49, 60-62 and 65-70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Note: for purposes of this rejection only, Examiner has interpreted the claims to be drawn to a method of detecting a loss of function of a nucleic acid encoding a regulatory

molecule comprising selecting a first nucleic acid molecule encoding a regulatory molecule, selecting a second set of nucleic acid molecules comprising sequences which are induced or repressed by the regulatory molecule encoded by the first nucleic acid molecule, hybridizing a transcription indicator of a test cell to a set of nucleic acid probes which comprise any portion of the nucleic acid molecules of the second set of nucleic acid molecules, detecting the amount of transcription indicator which hybridizes to each of said set of nucleic acid probes, and identifying the nucleic acid encoding the regulatory molecule as having a loss of function if (1) hybridization of the transcription indicator of the test cell to any probe(s) in the set which is(are) normally induced by the regulatory molecule is(are) lower than hybridization to the same probe(s) using a transcription indicator from a normal cell, or (2) hybridization of the transcription indicator of the test cell to any probe(s) in the set which is(are) normally repressed by the regulatory molecule is(are) higher than hybridization using a transcription indicator from a normal cell.

The claims are drawn to methods of detecting a loss of function of a nucleic acid encoding a regulatory molecule in a test cell wherein hybridization to a transcription indicator to a probe which comprises a portion of a nucleic acid which is

either induced or repressed by the regulatory molecule is either lower or higher than hybridization using a transcription indicator from a normal cell is indicative of a loss of function of the regulatory molecule. Some claims are further drawn to such methods wherein the regulatory molecule is p53 (claim 47). Some claims are further drawn to such a method wherein the test cell is a breast cell (claim 48) or to such a method wherein the induced or repressed genes are Bax, Cyclin G, GADD45, IGF-BP-3, $p21^{WAF1/CIP1}$, Thrombospondin, c-myc and PCNA. The claims encompass the use of any probe or set of probes as long as the probe(s) comprises a portion of the gene which is either repressed or induced by the regulatory molecule being tested. The claims encompass any regulatory molecule in any test cell. The claims do not provide any structural or functional information with regard to which test cells can be used with which portions of which genes such that a loss of function of a regulatory molecule can be determined. Thus, the rejected claims comprise a set of methods that are, at best, defined by the functional relationship between a regulatory molecule and its downstream targets.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the

genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The specification describes probes which can specifically hybridize to a sequence of interest and be of 5-500 nucleotides in length (page 25). The specification also describes the determination of "the function of p53 mutation" by monitoring the expression p53 up-regulated GADD45, cyclin G, $p21^{WAF1/CIP1}$, Bax, IGF-BP3, and Thrombospondin, and p53 down-regulated c-myc and PCNA between the HT-425 cell line derived from normal breast tissue peripheral to an infiltrating ductal carcinoma and malignant breast cancer cell lines (pages 41 and 46). No description is provided of such a method for test cells and regulatory molecules of any other type. No description is provided of which portions of the GADD45, cyclin G, $p21^{WAF1/CIP1}$, Bax, IGF-BP3, Thrombospondin, c-myc and PCNA genes were used for the hybridization to the "transcription indicator."

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claims with regard to structure and function, the examples are only representative of one method for identifying a loss of function of one regulatory molecule. The results are not necessarily

predictive of any other regulatory molecule used in combination with breast cancer cells or any other type of cell with probes comprising portions of down- or up-regulated genes such that a loss of function of the regulatory molecule can be identified. Thus it is impossible to extrapolate from the example described herein those regulatory molecules used in combination with the appropriate cells and probes such that the limitations of the rejected claims were met.

The prior art does not appear to offset the deficiencies of the instant specification in that it does not describe a set of regulatory molecules for which a loss of function can be determined based upon hybridization of a transcriptional indicator to the appropriate (set of) probes. Sanchez-Beato et al (*Journal of Pathology* **180**:58-64, 1996) describe the determination of a loss of function in p53 utilizing downstream genes MDM2 and $p21^{WAF1/CIP1}$, but Sanchez-Beato et al do not teach such a method wherein the loss of function is determined solely by hybridization to probes comprising a portion of those genes.

Given the very large genus of nucleic acid molecules encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to the methods fulfilling the claim limitations of claims 46-49, 60-62 and 65-70, the skilled artisan would not have been

able to describe the broadly claimed genus of cells, regulatory molecules and probes of down- or up-regulated genes of said regulatory molecules such that loss of function of the regulatory molecule is identified. Thus, there is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those cells used in conjunction with those probes of down- or up-regulated genes used in conjunction with those regulatory molecules that satisfy the functional limitations of the claims. Therefore, the skilled artisan would have reasonably concluded Applicant was not in possession of the claimed invention for claims 46-49, 60-62 and 65-70.

Claims 71-73, 85-86, 89-94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Note: for purposes of this rejection only, Examiner has interpreted the claims to be drawn to any a method of diagnosing

neoplasia in a test cell wherein the method encompasses the use of any mRNA, cDNA or cRNA transcriptional indicator, any probe set comprising nucleic acid probes which comprise any portion of genes induced or repressed by p53 in any test cell.

The claims are drawn to methods of diagnosing neoplasia of a test cell comprising hybridizing a transcription indicator of a test cell to a set of nucleic acid probes, detecting the amount of transcription indicator which hybridizes to each of said set of probes and identifying a test cell as neoplastic if (1) hybridization of the transcription indicator to a probe which is a p53-activited gene is lower in the test cell than hybridization using a transcription indicator from a normal cell or (2) hybridization of the transcription indicator of the test cell to a probe which is p53-repressed gene is higher than hybridization using a transcription indicator from a normal cell. Some claims are further limited to such a method wherein the test cell is a breast cell and wherein the probes comprise a portion of the genes for GADD45, cyclin G, $p21^{WAF1/CIP1}$, Bax, IGF-BP3, Thrombospondin, c-myc and PCNA. Some claims are further limited to such a method wherein the test cell is identified as neoplastic if hybridization is at least 3-fold, 5-fold or 10-fold different between compared samples. The claims encompass any test cell, the use of any transcription indicator as long as

the transcription indicator is mRNA, cDNA or cRNA, the use of any probe set as long as (1) hybridization of the transcription indicator of the test cell to a probe which is a p53-activiated gene is lower than hybridization using a transcription indicator from a normal cell, or (2) hybridization of the transcription indicator of the test cell to a probe which is a p53-repressed gene is higher than hybridization using a transcription indicator from a normal cell. The claims do not provide any structural information with regard to probe sequences or transcription indicators which can be used in combination with which test cells such that neoplasia of a test cell can be diagnosed. Thus, the rejected claims comprise a set of methods utilizing nucleic acid sequences, transcription indicators, and cells that are defined by the function of the sequences/cells.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The specification describes the use of expressed genes identified within the specification that "will find application in a wide array of

uses" including "diagnostic uses" (see, e.g., Example 3 on page 49, middle). The specification also describes genes which are p53 up-regulated: GADD45, cyclin G, $p21^{WAF1/CIP1}$, Bax, IGF-BP3, and Thrombospondin, and genes which are p53 down-regulated: c-myc and PCNA (Table 2, page 48). However, no description is provided of such a method for test cells of any kind. Nor does the description provide any structural information with regard to which other genes which are p53-regulated could be used or which probe sequences could be used with which transcription indicators.

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claims with regard to structure and function, the examples are only representative of one set of p53-regulated genes used in combination with one or two sets of transcription indicators from one or two types of cells. The results are not necessarily predictive of any other transcription indicator from any other test cells used in combination with any other probe set. Thus it is impossible to extrapolate from the examples described herein those nucleic acid molecules and test cells that would necessarily meet the structural/functional characteristics of the rejected claims.

The prior art does not appear to offset the deficiencies of the instant specification in that it does not describe a set of methods of diagnosing neoplasia in a test cell comprising hybridizing a transcription indicator of a test cell to a set of nucleic acid probes, detecting the amount of transcription indicator which hybridizes to each of said set of probes and identifying a test cell as neoplastic if (1) hybridization of the transcription indicator to a probe which is a p53-activited gene is lower in the test cell than hybridization using a transcription indicator from a normal cell or (2) hybridization of the transcription indicator of the test cell to a probe which is a p53-repressed gene is higher than hybridization using a transcription indicator from a normal cell. Velculescu et al (*Clinical Chemistry* **42**(6):858-868, 1996) note that "[a]lterations of the p53 gene result in defective cellular responses after DNA damage and predispose cells to dysregulated growth, tumor formation and progression, and potential resistance (of tumor cells) to certain chemotherapeutic agents or ionizing radiation" (see, e.g., Abstract on page 858). Velculescu et al also teach that GADD45, cyclin G, $p21^{WAF1/CIP1}$, Bax, IGF-BP3, Thrombospondin, c-myc and PCNA are among those genes which are transcriptionally regulated by p53 (see page 861, Table 2). However, Velculescu et al do not teach even the

use of p53 as a *direct* way to diagnose a cell as neoplastic, much less the use of indirect indicators such as downstream p53 transcriptional targets such as those listed above, in such a method.

Given the very large genus of nucleic acid molecules and test cells encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to the transcription indicators, probe sequences and test cells capable of fulfilling the claim limitations of claims 71-73, 85-86, 89-94, the skilled artisan would not have been able to describe the broadly claimed genus of probe sets, transcription indicators, and test cells used in a method such that the hybridization of the transcription indicator to probes comprising portions of p53-regulated genes could identify a cell as neoplastic. Thus, there is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those nucleic acid sequences (transcription indicators or probes) and those test cells that satisfy the functional limitations of the claims. Therefore, the skilled artisan would have reasonably concluded Applicant was not in possession of the claimed invention for claims 71-73, 85-86, 89-94.

Claims 71-73, 85-86, 89-94 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diagnosing a test cell as neoplastic for breast cancer cells, wherein both cells are of the same type or tissue and one cancer cell is suspected of being neoplastic, and wherein the transcription indicator comprises total mRNA from both of said cells and wherein the probes used are specific for GADD45, cyclin G, $p21^{WAF1/CIP1}$, Bax, IGF-BP3, Thrombospondin, c-myc and PCNA, does not reasonably provide enablement for a method of diagnosing neoplasia in a test cell wherein the method encompasses the use of any mRNA, cDNA or cRNA transcriptional indicator, any probe set comprising nucleic acid probes which comprise any portion of genes induced or repressed by p53 for any test cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims.

Note: for purposes of this rejection only, Examiner has interpreted the claims to be drawn to any a method of diagnosing neoplasia in a test cell wherein the method encompasses the use of any mRNA, cDNA or cRNA transcriptional indicator, any probe set comprising nucleic acid probes which comprise any portion of genes induced or repressed by p53 in any test cell.

Enablement is considered in view of the *Wands* factors (MPEP 2164.01(a)). These include: nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the quantity of experimentation necessary, the relative skill levels of those in the art, and the breadth of the claims. The most relevant *Wands* factors for evaluating the enablement of the instant rejection are discussed below.

Nature of the invention and Breadth of the Claims: The nature of the invention is complex and the breadth of the claims is wide. The invention is drawn to method of diagnosing neoplasia in a test comprising the use of any mRNA, cDNA or cRNA transcription indicator from any test cell used in combination with any set of probes wherein the probes comprise any portion of a gene or genes which are either activated or repressed by p53. Although some claims are further limited to a specific set of genes from which the probe sequences are comprised, the potential number of combinations of probes and transcription indicators and test cells is extremely large and exacerbates the complex nature of the invention. The invention is further complicated by the fact that the diagnostic test is indirect isofar as it identifies a test cell as neoplastic based on the

change in expression of a number of p53-regulated genes, wherein the change in expression of these genes is presumably indicative of altered p53 function.

State of the Art: At the time of filing, alterations in the p53 gene were known to result in defective cellular responses after DNA damage and to "predispose cells to dysregulated growth, tumor formation and progression, and potential resistance (of tumor cells) to certain chemotherapeutic agents or ionizing radiation" (Velculescu, et al. *Clinical Chemistry* **42**(6):858-868, 1996). At the time of filing, it was also known that GADD45, cyclin G, $p21^{WAF1/CIP1}$, Bax, IGF-BP3, Thrombospondin, c-myc and PCNA were among those genes transcriptionally regulated by p53. However, the art at the time of filing is silent with regard to the use of hybridization to a set of probes comprising portions of p53-induced or repressed genes as a means to determine whether or not a test cell was neoplastic.

The Amount of Direction or Guidance Present and the Presence of Working Examples: The specification describes the use of expressed genes identified within the specification that "will find application in a wide array of uses" including "diagnostic uses" (see, e.g., Example 3 on page 49, middle). The specification also describes genes which are p53 up-

regulated: GADD45, cyclin G, $p21^{WAF1/CIP1}$, Bax, IGF-BP3, and Thrombospondin, and genes which are p53 down-regulated: c-myc and PCNA (Table 2, page 48). However, no description is provided of a method for determining whether any given test cell is neoplastic based upon differences in hybridization of a transcription indicator to a probe set comprising portions of genes which are p53-activated or p53-repressed. Nor does the description provide any structural information with regard to which other genes which are p53-regulated could be used or which probe sequences could be used with which transcription indicators.

The Level of Unpredictability and The Amount of Experimentation Required: Given the undeveloped level in the state of the art with regard to methods for determining whether or not a test cell is neoplastic based upon hybridization to a set of p53-regulated genes, as well as the lack of guidance provided by both the state of the art and the instant disclosure, the level of unpredictability when reducing the large genus of instantly-claimed embodiments of the invention to practice is quite high. Furthermore, the underdeveloped state of the art, the lack of guidance provided by the specification and the prior art, and the high level of unpredictability in the art would require one of ordinary skill in the art to perform an

inordinate amount of trial-and-error experimentation in order to determine which probe sets could be used in combination with which transcription indicators from which cells such that a neoplastic cell could be identified.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 46-47, 49, 60 and 65-66 rejected under 35 U.S.C. 103(a) as being unpatentable over Sanchez-Beato et al (*Journal of Pathology* **180**:58-64, 1996) in view of Velculescu et al (*Clinical Chemistry* **42**(6):858-868, 1996).

Sanchez-Beato et al teach a method for detecting a functional mutation (loss of function mutation) in a target up-stream regulatory gene, comprising selecting the first nucleic acid encoding a regulatory molecule, i.e. p53, selecting a second set of nucleic acid molecules whose expression is induced or repressed by the regulatory molecule in normal cells, i.e.,

p21/WAF1/CIP1 and MDM2, hybridizing a transcription indicator of a test cell to a set of nucleic acid probes, wherein the transcription indicator is cDNA, detecting the amount of transcription indicator which hybridizes to the probe and identifying a test cell as having lost function of the regulatory molecule if hybridization of the transcription indicator of the test cell to the probe comprising a portion of a nucleic acid induced by p53 is lower than hybridization using a transcription indicator from a normal cell (see entire document, especially page 58, second column, first sentence; paragraph bridging pages 60-61; and page 63, Figure 4). Sanchez-Beato et al further teach detection of a plurality of p53 downstream genes including p21/WAF1/CIP1 and PCNA in addition to MDM2 to obtain reference and target expression patterns and compare said target and reference expression patterns to detect a functional mutation of said regulatory molecule (see, e.g., page 60, Figure 1; page 61, Figure 2; and page 60, right column, first full paragraph). Sanchez-Beato et al further teach that loss of wild-type p53 function precludes overexpression of MDM2 and p21 because high levels of MDM2 and p21 are seen in association with wild-type p53 (page 63, second column, lines 6-9). Sanchez-Beato teach the downstream genes of

p53 comprise p53 upregulated p21/WAF1/CIP1 and p53-downregulated PCNA (page 58, left column).

Sanchez-Beato et al do not teach such a method where the set of nucleic acid probes comprise nucleic acid sequences which comprise a portion of at least four genes which are activated by p53. Nor do Sanchez-Beato et al teach such a method wherein for probes set comprises a portion of the GADD45, cyclin G, $p21^{WAF1/CIP1}$, Bax, IGF-BP3, Thrombospondin, c-myc and PCNA genes.

Velculescu et al teach GADD45, cyclin G, $p21^{WAF1/CIP1}$, Bax, IGF-BP3, Thrombospondin, c-myc and PCNA as p53-regulated genes.

It would have been *prima facie* obvious for one of ordinary skill in the art to have modified the method of Sanchez-Beato et al with the teachings of Velculescu et al because Sanchez-Beato et al teach the use of p53-regulated genes in a method of testing for a loss of function in a nucleic acid encoding p53 and Velculescu et al teach GADD45, cyclin G, $p21^{WAF1/CIP1}$, Bax, IGF-BP3, Thrombospondin, c-myc and PCNA as p53-regulated genes.

One of ordinary skill in the art would have been motivated to use the p53 regulated genes taught by Velculescu et al in the method taught by Sanchez-Beato et al because the ordinary skilled artisan would have known that the resulting expression profile would have been significantly more informative with

eight genes than it would have been with only two in the profile.

Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result when combining the teachings of Sanchez-Beato et al with those of Velculescu et al.

Claims 46-47, 49, 60-62 and 65-66 rejected under 35 U.S.C. 103(a) as being unpatentable over Sanchez-Beato et al (*Journal of Pathology* **180**:58-64, 1996) in view of Velculescu et al (*Clinical Chemistry* **42**(6):858-868, 1996) and further in view of Brown et al (US Patent No. 5,807,522).

Briefly, Sanchez-Beato et al in view of Velculescu et al teach a method for detecting a functional mutation (loss of function mutation) in a target up-stream regulatory gene, comprising selecting the first nucleic acid encoding a regulatory molecule, i.e. p53, selecting a second set of nucleic acid molecules whose expression is induced or repressed by the regulatory molecule in normal cells, i.e., GADD45, cyclin G, $p21^{WAF1/CIP1}$, Bax, IGF-BP3, Thrombospondin, c-myc and PCNA, hybridizing a transcription indicator of a test cell to such a set of nucleic acid probes, wherein the transcription indicator

is cDNA, detecting the amount of transcription indicator which hybridizes to the probe and identifying a test cell as having lost function of the regulatory molecule if hybridization of the transcription indicator of the test cell to the probe comprising a portion of a nucleic acid induced by p53 is lower than hybridization using a transcription indicator from a normal cell.

Sanchez-Beato et al in view of Velculescu et al do not teach such a method wherein the nucleic acid probes are attached to a solid support or wherein the nucleic acid *probes* are arranged in an array.

Brown et al teach methods and an apparatus for forming microarrays of at least 10^3 distinct polynucleotide samples on a solid support (see entire document, including the Abstract and column 4, lines 16-23). Brown et al further teach a method of detecting a mutation in a disease gene comprising hybridizing amplified nucleic acid samples from different patients onto an array comprising nucleic acid probes attached to a solid support (see entire document, especially column 13, lines 1-45; and column 15, lines 19-43). Brown et al teach that such a procedure could be used to detect a disease gene mutation in multiple samples more quickly and efficiently than was

previously possible and would result in "significant time and cost savings" (see, e.g., column 15, lines 39-43).

It would have been *prima facie* obvious for one of ordinary skill in the art to combine the teachings of Brown et al with those of Sanchez-Beato et al in view of Velculescu et al because Sanchez-Beato et al in view of Velculescu et al teach a method of detecting a loss of function in a nucleic acid encoding a disease gene (p53) by detecting hybridization levels of transcription indicators to probes comprising portions of p53-regulated genes and Brown et al teach that transcription indicators from multiple samples can be used in a method of hybridization to probes comprising portions of 10^3 genes in a method of detecting a mutation in a disease gene.

One of ordinary skill in the art would have been motivated to combine the teachings of Sanchez-Beato et al in view of Velculescu et al with those of Brown et al for the expected benefit of testing the expression of multiple genes all at the same time and for the concomitant savings in cost and time as taught by Brown et al.

Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result when combining the teachings of Sanchez-

Beato et al in view of Velculescu et al with those of Brown et al.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 71, 86, 89 & 91 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 12 & 23-24 of U.S. Patent No. 6,171,798. Although the conflicting claims are not identical,

they are not patentably distinct from each other because the instant claims are genus claims to the patent claims' species insofar as the instant claims encompass methods of diagnosing neoplasia in a test cell comprising hybridizing any transcription indicator to probes comprising a portion of any gene activated or repressed by p53 and using the level of hybridization of the transcription indicator to the probes in the set as means of identifying a test cell as neoplastic, whereas the pending claims are drawn to a subset of genes which are p53-regulated, including GADD45 and IGF-BP3. Furthermore, the instant claims are drawn to the use of any two samples, whereas the patented claims require the use of a test sample and a normal sample wherein the samples are of the same tissue type and wherein the first sample is suspected of being neoplastic. However, the patented claims are genus claims to the instant claims' species insofar as the patented claims are also drawn to diagnosing cancer and to determining p53 status in a sample, not just determining whether a cell is neoplastic.

Claims 46-47, 49, 60, 65-66 and 68-69 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 and 6-7 of U.S. Patent No. 6,303,301. Although the conflicting claims are not identical,

they are not patentably distinct from each other because the instant claims are genus claims to the patented claims' species insofar as the instant claims encompass methods for determining loss of function of any regulatory molecule, not just p53.

Claims 46-47, 49, 60, 62, 65-70 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 6 and 8-15 of U.S. Patent No. 6,733,969. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are genus claims to the patented claims' species insofar as the instant claims encompass methods for determining loss of function of any regulatory molecule in any test sample (not just between samples having wild-type up-stream regulatory molecules). However, the patented claims can use any method of transcript expression detection whereas the instant claims utilize hybridization to probe sets.

Conclusion

No claims are allowed.

Certain papers related to this application may be submitted to the Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94

(December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is (571) 273-8300. Note: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent applications to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should be directed to Walter Schlapkohl whose telephone number is (571) 272-4439. The examiner can normally be reached on Monday through Thursday from 8:30 AM to 6:00 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached at (571) 272-0781.

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Patent Examiner
Art Unit 1636

May 28, 2006

NANCY VOGEL
PRIMARY EXAMINER